February 1, 1949.

Dr. C. N. Hinshelwood,
Physical Chemistry Laboratory,
Oxford University,
England.

Dear Dr. Hinshelwood,

As you may imagine, I have read your paper with A. F. Peacocke with great interest. (The changes induced in B. lactis aerogenes by irradiation with ultra-violet light, PRS B135:454-461 1948.) I am not sure to what extent your experiences parallel ours, but I have no doubt that more or less temporary effects, along the lines that have been called "Dauermodifications" do occur and that these may be based on quantitative alterations in an autosynthetic enzyme system. Such a system is, after all, a version of the proposal for "plasmagenic inheritance" which is now so popular in a great many genetic circles.

On the other hand, I feel that our studies on character recombination, and especially ~~ohr~~very recent observations on segregation and recombination from certain heterozygous diploid lines of E. coli, are very compelling to the notion of a gene system in this organism which is entirely comparable to that in higher forms.

May I point out that the origin of a bacterial population from a single cell or colony in no way precludes the possibility of the

action of natural selection in such a population, unless the occurrence of mutation be denied. In fact whatever the basic nature of the variation, be it genic mutation or adaptation in your sense, any factor which results in transmissible differences betweenncells in a population must be expected to result in natural selection in favor of those cells, and their progeny, which are best suited to their local environment.

May I point out further that there should be no repugnance at the concept of reverse-mutations for nutritional requirements. They have been found by a number of workers to account for the "training" to growth in a synthetic medium exhibited by a number of Neurospora mutants. The genetic analysis here is beyond question. On the other hand, it may be mentioned that in a few instances, the analysis of such training has led to the tentative conclusion that a biochemical mutation, undoubtedly genic, might be compensated for by a non-genic mechanism, therefore somewhere in the arena of cytoplasmic or autosynthetic enzyme effects.

Finally, a word about our biochemical mutants. The majority of the cultures we have used in our genetic studies are quite stable, and whichinoculated reasonably lightly (say 10^3 - 10^4 cells) into deficient media show a complete dependance on the relevant growth factor. Such inocula will remain viable for many days, or weeks but will not proliferate unless or until such growth factors are added. When very large inocula are used, it is only to be expected that we would reveal a very small proportion (ca. 10^{-6} or 10^{-7} in most strains) of cells which are independent of the growth factor. It is perfectly plain that natural selection is acting when one discovers a few dozen colonies developing on a synthetic agar plate into which a billion organisms had been inoculated. But from the point of view of a genetic analysis, it would scarcely matter if the mutants differed from wild type only in the lag period before growth. Such a difference would still constitute a character which would be valid

for genetic study. But because such characters might be perhaps a bit vague or variable, we have avoided them.

I would appreciate it greatly if you could find it possible to keep me up to date on your work and stimulating ideas by an exchange of publications. I received a very few reprints sevetal years ago.

Yours sincerely,

Joshua Lederberg,
Assistant Professor of Genetics.